

Sub B1
81. A modified wild-type human thyroid stimulating hormone (TSH) having increased TSH activity compared to wild-type human TSH comprising an α -subunit and a β -subunit, said α -subunit comprising at least three basic amino acids in the α -subunit at positions selected from the group consisting of positions 11, 13, 14, 16, 17, and 20.

82. The modified wild-type human TSH of Claim 81, said α -subunit further comprising a fourth basic amino acid at a position selected from the group consisting of positions 11, 13, 14, 16, 17, and 20.

83. The modified wild-type human TSH of Claim 82, wherein the basic amino acids of the α -subunit are at positions 11, 13, 16, and 20.

84. The modified wild-type human TSH of Claim 82, wherein the basic amino acids of the α -subunit are at positions 11, 13, 17, and 20.

85. The modified wild-type human TSH of Claim 82, wherein the basic amino acids of the α -subunit are at positions 13, 14, 16, and 20.

86. The modified wild-type human TSH of Claim 82, wherein the basic amino acids of the α -subunit are at positions 13, 14, 17, and 20.

87. The modified wild-type human TSH of Claim 82, said α -subunit further comprising a fifth basic amino acid at a position selected from the group consisting of positions 11, 13, 14, 16, 17, and 20.

A2
88. The modified wild-type human TSH of Claim 87, wherein the basic amino acids of the α -subunit are at positions 13, 14, 16, 17, and 20.

89. The modified wild-type human TSH of Claim 87, wherein the basic amino acids of the α -subunit are at positions 11, 13, 14, 16, and 20.

90. The modified wild-type human TSH of Claim 81, wherein the basic amino acids of the α -subunit are at positions 11, 13, 14, 16, 17, and 20.

91. The modified wild-type human TSH of Claim 81, wherein the basic amino acids of the α -subunit are at positions 13, 16, and 20.

92. The modified wild-type human TSH of Claim 81, further modified so that said β -subunit comprises a basic amino acid in the β -subunit in at least one position selected from the group consisting of positions 58, 63, and 69.

Appl. No. : 9/185,408
Filed : November 3, 1998

93. The modified wild-type human TSH of Claim 92, wherein the basic amino acids of the β -subunit are at positions 58, 63, and 69.

94. The modified wild-type human TSH of Claim 92, wherein a basic amino acid of the β -subunit is at position 58.

95. The modified wild-type human TSH of Claim 92, wherein a basic amino acid of the β -subunit is at position 63.

96. The modified wild-type human TSH of Claim 92, wherein a basic amino acid of the β -subunit is at position 69.

97. The modified wild-type human TSH of Claim 81, wherein the basic amino acids are selected from the group consisting of lysine and arginine.

98. A nucleic acid encoding the modified wild-type human TSH α -subunit of Claim 81.

19 99. A vector comprising the nucleic acid of Claim 98, wherein the vector is suitable for expressing the nucleic acid.

20 100. A host cell comprising the vector of Claim 99, wherein the host cell is suitable for expressing the nucleic acid.

Sub B2
A2
Cont
101. The modified wild-type human TSH of Claim 81, further modified so that said modified wild-type human TSH has less than five amino acid substitutions in said α -subunit in positions other than positions 11, 13, 14, 16, 17, and 20.

102. The modified wild-type human TSH of Claim 81, further modified so that said modified wild-type human TSH has less than four amino acid substitutions in said α -subunit in positions other than positions 11, 13, 14, 16, 17, and 20.

103. The modified wild-type human TSH of Claim 81, further modified so that said modified wild-type human TSH has less than three amino acid substitutions in said α -subunit in positions other than positions 11, 13, 14, 16, 17, and 20.

104. The modified wild-type human TSH of Claim 81, further modified so that said modified wild-type human TSH has less than two amino acid substitutions in said α -subunit in positions other than positions 11, 13, 14, 16, 17, and 20.

105. The modified wild-type human TSH of Claim 81, further modified so that said modified wild-type human TSH has complete amino acid sequence homology with

Appl. No. : 09/185,408
Filed : November 3, 1998

the corresponding wild-type human TSH in said α -subunit in positions other than positions 11, 13, 14, 16, 17, and 20.

106. A modified wild-type human thyroid stimulating hormone (TSH) having increased TSH activity compared to wild-type human TSH comprising an α -subunit and a β -subunit, said α -subunit comprising a basic amino acid in the α -subunit in at least one position selected from the group consisting of positions 11, 13, 14, 16, 17, and 20.

107. The modified wild-type human TSH of Claim 106, wherein a basic amino acid of the α -subunit is at position 11.

108. The modified wild-type human TSH of Claim 106, wherein a basic amino acid of the α -subunit is at position 13.

109. The modified wild-type human TSH of Claim 106, wherein a basic amino acid of the α -subunit is at position 14.

110. The modified wild-type human TSH of Claim 106, wherein a basic amino acid of the α -subunit is at position 16.

111. The modified wild-type human TSH of Claim 106, wherein a basic amino acid of the α -subunit is at position 17.

112. The modified wild-type human TSH of Claim 106, wherein a basic amino acid of the α -subunit is at position 20.

113. The modified wild-type human TSH of Claim 106, wherein the basic amino acid is selected from the group consisting of lysine and arginine.

114. The modified wild-type human TSH of Claim 106, further modified so that said α -subunit comprises a basic amino acid in at least two positions selected from the group consisting of positions 11, 13, 14, 16, 17, and 20.

115. The modified wild-type human TSH of Claim 114, wherein the basic amino acids of the α -subunit are at positions 16 and 20.

116. The modified wild-type human TSH of Claim 114, wherein the basic amino acids of the α -subunit are at positions 16 and 13.

117. The modified wild-type human TSH of Claim 114, wherein the basic amino acids of the α -subunit are at positions 20 and 13.

*Sub
B2
cont.*

*2
cont.*

A

Appl. No. : 09/185,408
Filed : November 3, 1998

118. The modified wild-type human TSH of Claim 114, wherein the basic amino acid is selected from the group consisting of lysine and arginine.

119. The modified wild-type human TSH of Claim 106, further modified so that said β -subunit further comprises a basic amino acid in the β -subunit in at least one position selected from the group consisting of positions 58, 63, and 69.

120. The modified wild-type human TSH of Claim 119, wherein the basic amino acids of the β -subunit are at positions 58, 63, and 69.

121. The modified wild-type human TSH of Claim 119, wherein a basic amino acid of the β -subunit is at position 58.

122. The modified wild-type human TSH of Claim 119, wherein a basic amino acid of the β -subunit is at position 63.

123. The modified wild-type human TSH of Claim 119, wherein a basic amino acid of the β -subunit is at position 69.

124. A nucleic acid encoding the modified wild-type human TSH α -subunit of Claim 106.

45/125. A vector comprising the nucleic acid of Claim 124, wherein the vector is suitable for expressing the nucleic acid.

46/126. A host cell comprising the vector of Claim 125, wherein the host cell is suitable for expressing the nucleic acid.

127. The modified wild-type human TSH of Claim 106, further modified so that said modified wild-type human TSH has less than five amino acid substitutions in said α -subunit in positions other than positions 11, 13, 14, 16, 17, and 20.

128. The modified wild-type human TSH of Claim 106, further modified so that said modified wild-type human TSH has less than four amino acid substitutions in said α -subunit in positions other than positions 11, 13, 14, 16, 17, and 20.

129. The modified wild-type human TSH of Claim 106, further modified so that said modified wild-type human TSH has less than three amino acid substitutions in said α -subunit in positions other than positions 11, 13, 14, 16, 17, and 20.

130. The modified wild-type human TSH of Claim 106, further modified so that said modified wild-type human TSH has less than two amino acid substitutions in said α -subunit in positions other than positions 11, 13, 14, 16, 17, and 20.